CS 6824: Application of Basic Clustering Algorithms to Find Expression Modules in Cancer

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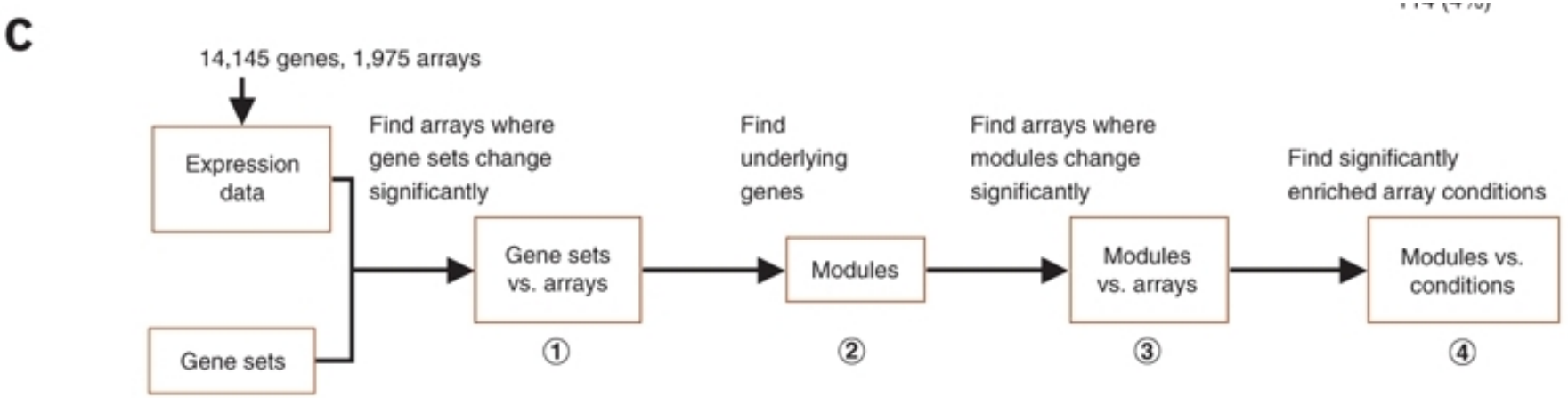
February 16, 2011

Innovative Application of Hierarchical Clustering

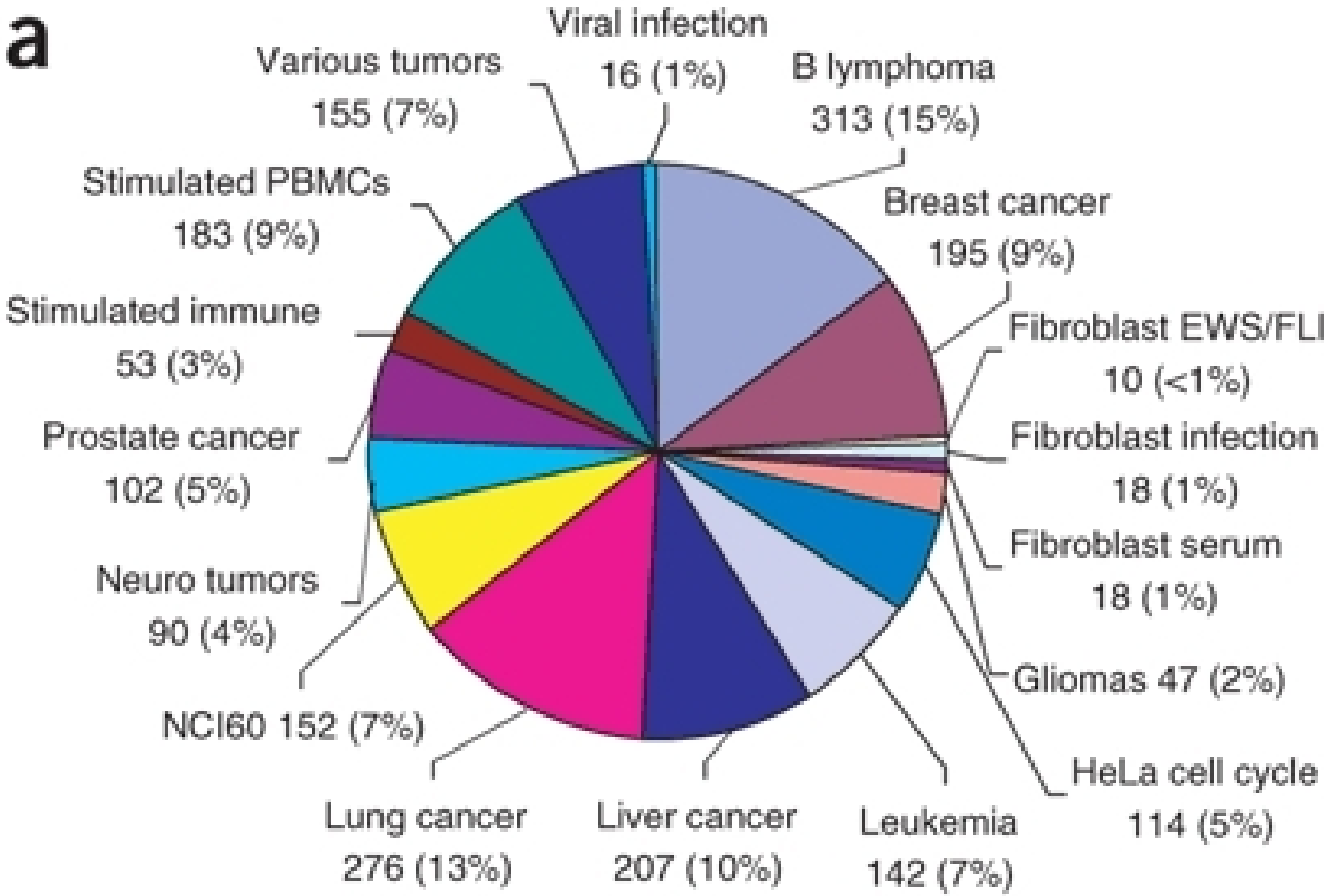
- *A module map showing conditional activity of expression modules in cancer*, Eran Segal, Nir Friedman, Daphne Koller and Aviv Regev, Nature Genetics 36, 1090–1098, 2004
- Analyse gene expression data to find groups of genes expressed in concert between different cancers.
- Use hierarchical clustering innovatively.

Key Ideas



- Group genes into predefined *gene sets*, e.g., groups of genes with the same functional annotation.
- Convert gene-by-array matrix into gene-set-by-array matrix.
- Hierarchically cluster gene sets in this matrix.
- Identify "interesting" gene set clusters (nodes) in the tree.
- In each gene set cluster, remove genes not expressed consistently with the cluster.

Gene Expression Data Sets



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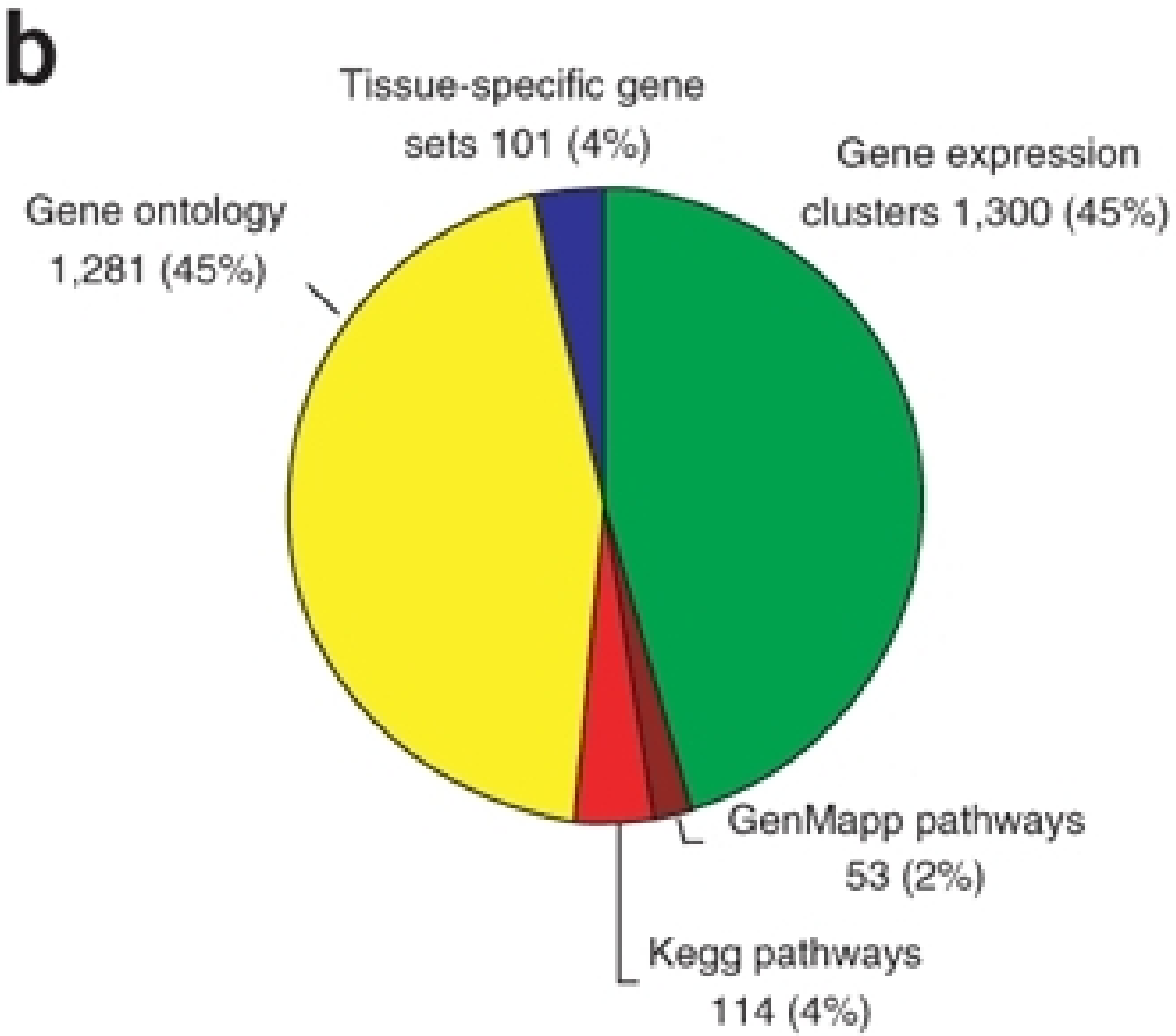
Pre-defined Gene Sets



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- A gene is *induced* (respectively, *repressed*) in an array if its log-fold change in expression is ≥ 1 (respectively, ≤ -1).
- For each gene set-array pair, compute the fraction of genes induced or repressed.
- Use these values in the gene-set-by-array matrix.

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- Statistical test: for a given array, is the fraction of induced genes in a gene set much larger than the fraction of induced genes in the entire array?
- Compute the p-value of the fraction using Fisher's exact test.
- Do so for every gene-set-array pair.
- Use false discovery rate correction to account for testing multiple hypotheses.
- Replace insignificant entries by 0.

Computing the Significance of an Entry in the Gene-Set-By-Array Matrix

- Let m be the number of genes in the data set.
- let m_G be the number of genes in a gene set G.
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- If this probability is at most a user-specified threshold, we deem that entry to be statistically significant.

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- Which nodes do we select as clusters in the tree?
  - Associate each interior node with Pearson correlation between the two children.
  - Cluster $\equiv$ node whose Pearson correlation differs by more than 0.05 from the Pearson correlation of its parent.

Turning Clusters into Modules

- Each cluster is the union of descendant gene sets (leaves).
- Module $\equiv$ Cluster minus genes whose expression is not consistent with the rest of the cluster.

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- No contribution from an array in I (or R) is g is not induced (or not repressed) in a.
- Larger contribution from arrays with fewer induced genes.
- Compute statistical significance of this score.

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- Random variable takes the value $-\log(p_a)$ with probability p_a and the value 0 with the probability $1 - p_a$.

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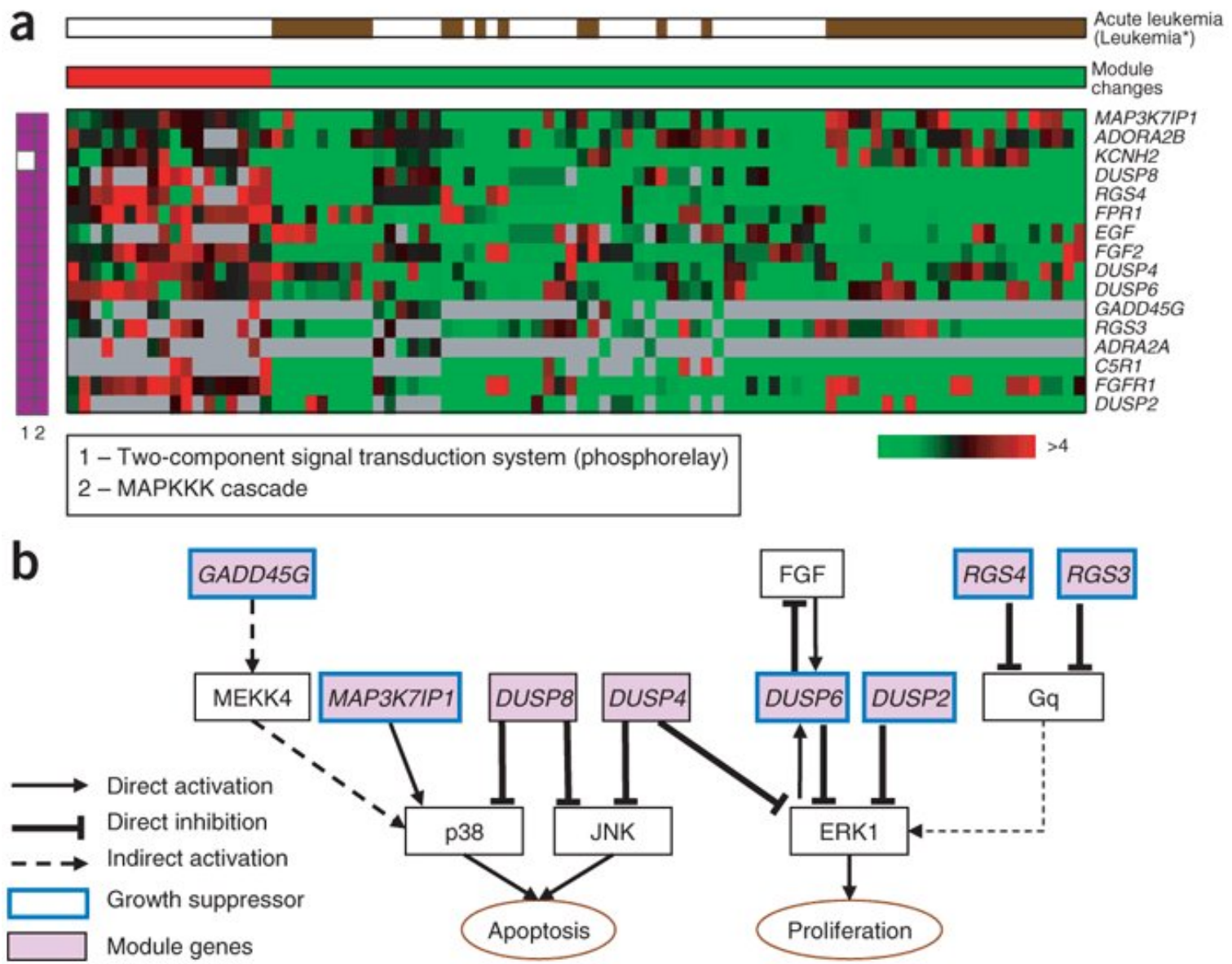
- Central limit theorem $\Rightarrow$ that the distribution of Score(g) is well-approximated by a Gaussian distribution with this mean and variance.
- Assess statistical significance by computing the tail of this Gaussian.

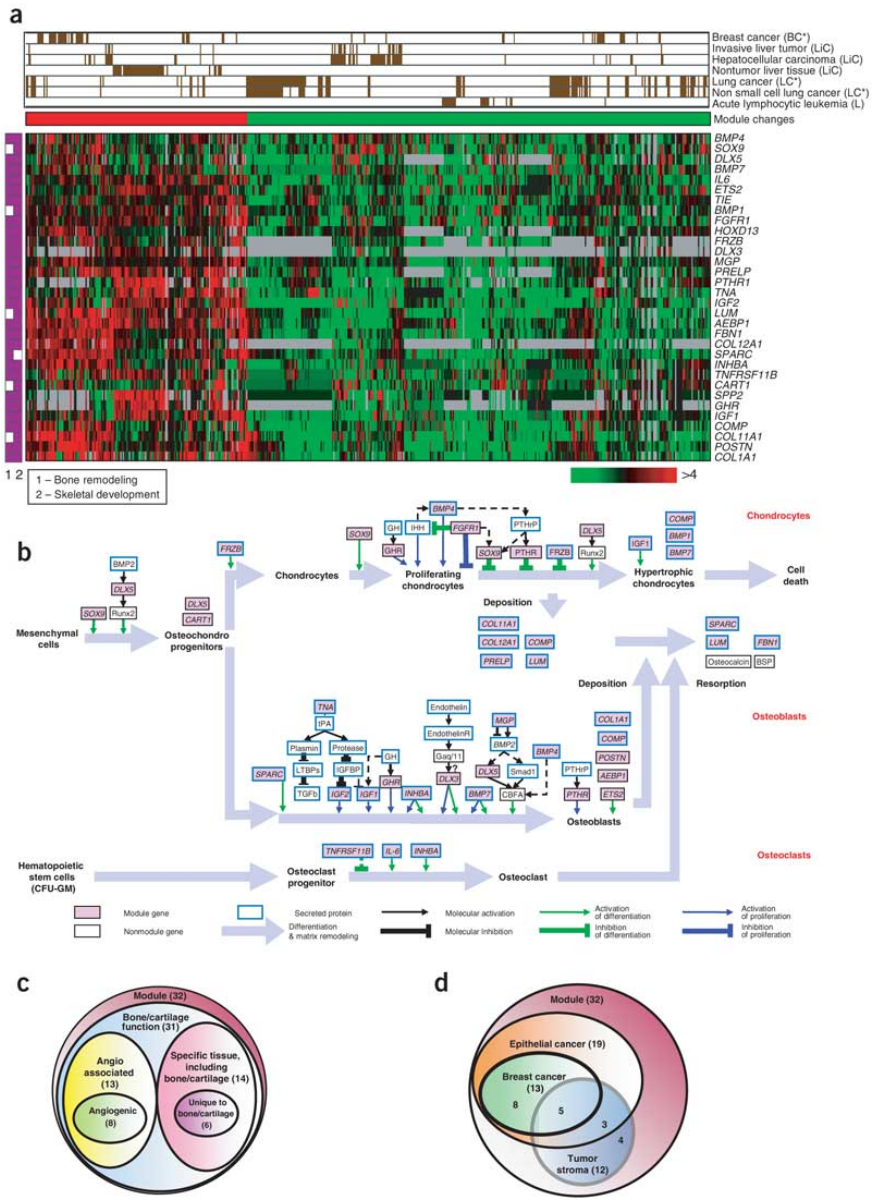
Further Analysis

- Statistical significance of computed modules using leave-one-out cross validation (read supplement).
- Compute enrichment of clinical annotations of the arrays in a module.
- Visualisation of modules.
- Literature-based analysis of modules

Growth Inhibitory Module



Bone Osteoblastic Module



Conclusions

- Used pre-defined gene sets to drive hierarchical clustering algorithm.
- Remove genes from a cluster of gene sets if the gene's expression profile deviates from the cluster.
- Automatically decide which arrays are part of a module.
- Interpretation of each module requires a lot of manual analysis.
- Such manual analysis is required for deciding subsequent experiments.